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10/804,470	03/18/2004	Henrik Stender	58576 (48497)	7227

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EXAMINER	
WONG, JENNIFER SHIN SHIN	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 05/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/804,470	STENDER ET AL.	
	Examiner	Art Unit	
	Jennifer Wong	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *22-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☒ Claim(s) *13* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I in the reply filed on February 3, 2006 is acknowledged. The traversal is on the ground(s) that there is no undue burden to search for the polynucleotides of Group II with the methods of Group I. This is not found persuasive because a search for the nucleic acids of Group II is not required to practice the methods of Group I. The nucleic acids of Group II can be used in a materially different process such as the synthesis of nucleic acids or proteins as well as for diagnostic therapies. As a result, a search for the methods for analysis of a target sequence of Group I is not co-extensive with the nucleic acids of Group II. A finding that the method of Group I is anticipated or obvious over the prior art would not necessarily extend to a finding that the nucleic acids of Group II are also anticipated or rendered obvious by the prior art. Similarly, a finding that the method of Group I are novel and unobvious over the prior art would not necessarily extend to a finding that the nucleic acids of Group II are also novel and unobvious over the prior art.

2. Claims 22-38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on February 6, 2006.

The requirement is still deemed proper and is therefore made FINAL.

Claim Objections

3. Claim 4 is objected to because of the following informalities: it refers to "the method of claims 1" in line 1. However, there is only one claim 1. The claim should be amended to recite "the method of claim 1." Appropriate correction is required.

4. Claim 13 is objected to because of the following informalities: Claim 13 is dependent on itself.

Specification

5. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. See page 15, line 13.

6. The use of the trademark LightCycler on page 4, line 12 has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1, 12, 13, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heller (U.S. Patent No. 5,532,129, published July 1996) in view of Elsas et al (U.S. Patent No. 6,207,387, published March 27, 2001).

Heller teaches a method to detect target sequences, wherein the method comprises step a) hybridizing two probes, wherein one probe has a fluorophore (Probe A) and another probe that has a quencher (Probe B) that hybridizes adjacent to Probe A; and method step b) the subsequent detection of Probe A's fluorescence as an indication of the presence of a target sequence.

With respect to claim 1, method step 1, Heller teaches a method comprising contacting two probes with a configuration wherein Probe A is labeled with a donor group at its 3' terminus and Probe B is labeled with an acceptor at its 5' terminus, and are hybridized adjacent to one another (Figure 1B, claim limitation 12). Heller's method includes "hybridization [of the probes] to the target sequence ... the fluorescent donor group...and acceptor group to a preselected donor-acceptor transfer distances so that when the system is irradiated by photonic energy at hv_1 the donor group absorbs the energy and transfers it...to the acceptor group which re-emits at (hv_2)," wherein Probes A and B have donor and acceptor groups respectively (column 4, lines 24-31). Heller teaches Probe B's acceptor group is a quencher and "use of quencher chromophore (or quencher)...has the capacity to accept...the transfer of energy...but does not have significant emission (column 6, lines 63-67 through column 7, lines 1-9). Thereby, Probe B's quenching group results in the lack of emission (hv_2). Accordingly, Heller teaches a 3' fluorophore, or donor, at the 3' termini of Probe A, and quencher, or acceptor, at the 5' end of Probe B. Furthermore, Heller teaches another configuration of the placement of the fluorophore and quencher groups on Probes A and B. Heller teaches Probes A and B can be labeled internally and spacing between the donor and

acceptor groups can be from 0-7 basepairs (column 10, lines 12-14 and 34-35; column 11, lines 17-19, claim limitation 13). Heller teaches that the probes can be configured in that there is "any chromophore can be paired with another chromophore to form an acceptor-donor pair, so long as the two chromophores have different emission spectrums," wherein the choromphores are defined as either fluorphores or quenchers (column 7, lines 2-11 and 32-34).

With respect to method step b, Heller teaches the level of hybridization to the target sequences is measured by the amount of Probe A's fluorescence. Heller teaches "relative efficiencies for the energy transfer process can be expressed...in terms of the ratio of transferred energy to the energy absorbed by the donor; this is determined by measuring the relative amount of donor fluorescence quenching that occurs in the presence of the acceptor" (column 6, lines 27-32).

However, Heller does not teach a method wherein the probes have wanted and unwanted sequences.

Elsas teaches of anchor and detection probes that detect mutations. Elsas teaches determining different mutations "can be achieved by using oligonucleotides...by attaching different detectable moieties, such as fluorescent, chemiluminescent, bioluminescent...to the oligonucleotides" (column 10, lines 43-47). Elsas teaches anchor and detection probes, wherein the "anchor probe forms one half of the detection probe set and carries a fluorescence quencher. The other half of the probe set has the allele-specific sequence. When the allele specific probe and the anchor probe are hybridized, the fluorescence is quenched" (column 11, lines 2-7). Detection probes are

designed for a wherein "the lower case letter represents the nucleotide that is different between the mutated and wild-type alleles" (column 10, lines 63-67 through column 11, lines 1-7). Thus, Probe A is the detection probe because it has both "wanted" and "unwanted" sequences, wherein the "wanted" sequence, the nucleotide of interest represented by the lowercase letter, and the sequences flanking the lower case letter is the "unwanted" sequences that correspond to the wildtype sequence. Similarly, Probe B is represented by the anchor probe because it has a quencher which hybridizes to the wild-type sequence, or "unwanted" region. The detection probe, Probe A, inherently has a fluorophore because the anchor probe quenches fluorescence during hybridization.

It would have been prima facie obvious at the time the invention was made for the ordinary artisan to modify the teachings of Heller with the improvement of designing probes with wanted and unwanted sequences taught by Elsas. Heller teaches detecting the presence of a target sequence by the amount of fluorescence of hybridized probes to said target whereby photonic mechanisms have been used "in an effort to impart sensitive fluorescent detection properties into DNA probe diagnostics" for "clinical diagnostic assays" whereas Elsas teaches allele specific probe designed for both "wanted" and "unwanted" sequences (Heller, column 2, lines 66-67 through column 3, lines 1-3). Elsas teaches "certain mutations [can] cause a mild disease, while others cause severe effects. Identifying the mutation is necessary to make diagnosis, initiate appropriate therapy, [and] estimate prognosis" (column 2, lines 5-9). One skilled in the art at the time the invention was made would have been motivated to have used Heller's

method with the allele-specific probe design of Elsas in order to have achieved the benefit of detecting mutations that are associated with disease with a sensitive clinical diagnostic assay. The skilled artisan would have also been motivated to use this improved method in order to diagnose diseases, predict prognosis, and prescribe an appropriate treatments with a sensitive assay (Heller, column 2, lines 66-67 through column 3, lines 1-3; and Elsas column 2, lines 5-9; claim limitation 21).

8. Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Heller (U.S. Patent No. 5,532,129, published July 1996) in view of Elsas et al (U.S. Patent No. 6,207,387, published March 27, 2001) and in further view of Meade et al. (U.S. PGPUB 2001/0046679, published November 29, 2001).

Heller teaches a method to detect target sequences, wherein the method comprises step a) hybridizing two probes, wherein one probe has a fluorophore (Probe A) and another probe that has a quencher (Probe B) that hybridizes adjacent to Probe A; and method step b) the subsequent detection of Probe A's fluorescence as an indication of the presence of a target sequence.

With respect to method step 1, Heller teaches a method comprising contacting two probes with a configuration wherein Probe A is labeled with a donor group at its 3' terminus and Probe B is labeled with an acceptor at its 5' terminus, and are hybridized adjacent to one another (Figure 1B). Heller's method includes "hybridization [of the probes] to the target sequence ... the fluorescent donor group...and acceptor group to a preselected donor-acceptor transfer distances so that when the system is irradiated by

photonic energy at hv_1 the donor group absorbs the energy and transfers it...to the acceptor group which re-emits at (hv_2)," wherein Probes A and B have donor and acceptor groups respectively (column 4, lines 24-31). Heller teaches Probe B's acceptor group is a quencher and "use of quencher chromophore (or quencher)...has the capacity to accept...the transfer of energy...but does not have significant emission (column 6, lines 63-67 through column 7, lines 1-9). Thereby, Probe B's quenching group results in the lack of emission (hv_2). Accordingly, Heller teaches a 3' fluorophore, or donor, at the 3' termini of Probe A, and quencher, or acceptor, at the 5' end of Probe B. Furthermore, Heller teaches another configuration of the placement of the fluorophore and quencher groups on Probes A and B. Heller teaches Probes A and B can be labeled internally and spacing between the donor and acceptor groups can be from 0-7 basepairs (column 10, lines 12-14 and 34-35; column 11, lines 17-19). Heller teaches that the probes can be configured in that there is "any chromophore can be paired with another chromophore to form an acceptor-donor pair, so long as the two chromophores have different emission spectrums," wherein the choromphores are defined as either fluorophores or quenchers (column 7, lines 2-11 and 32-34).

With respect to method step b, Heller teaches the level of hybridization to the target sequences is measured by the amount of Probe A's fluorescence. Heller teaches "relative efficiencies for the energy transfer process can be expressed...in terms of the ratio of transferred energy to the energy absorbed by the donor; this is determined by measuring the relative amount of donor fluorescence quenching that occurs in the presence of the acceptor" (column 6, lines 27-32).

However, Heller does not teach a method wherein the probes have wanted and unwanted sequences, and a fluorophore at the 3' terminus of Probe B.

Elsas teaches of anchor and detection probes that detect mutations. Elsas teaches determining different mutations "can be achieved by using oligonucleotides...by attaching different detectable moieties, such as fluorescent, chemiluminescent, bioluminescent...to the oligonucleotides" (column 10, lines 43-47). Elsas teaches anchor and detection probes, wherein the "anchor probe forms one half of the detection probe set and carries a fluorescence quencher. The other half of the probe set has the allele-specific sequence. When the allele specific probe and the anchor probe are hybridized, the fluorescence is quenched" (column 11, lines 2-7). Detection probes are designed for a wherein "the lower case letter represents the nucleotide that is different between the mutated and wild-type alleles" (column 10, lines 63-67 through column 11, lines 1-7). Thus, Probe A is the detection probe because it has both "wanted" and "unwanted" sequences, wherein the "wanted" sequence, the nucleotide of interest represented by the lowercase letter, and the sequences flanking the lower case letter is the "unwanted" sequences that correspond to the wildtype sequence. Similarly, Probe B is represented by the anchor probe because it has a quencher which hybridizes to the wild-type sequence, or "unwanted" region. The detection probe, Probe A, inherently has a fluorophore because the anchor probe quenches fluorescence during hybridization.

Meade et al teaches probes that have an acceptor at its 5' terminus and a donor at its 3' terminus (Figures 1_B, D, F and H). Meade teaches "single stranded nucleic

acids with at least one...donor moiety and one...acceptor moiety which hybridize to regions with exact matches can be used as controls for the presence of the target sequence" (page 11, left column, paragraph 0123).

It would have been prima facie obvious at the time the invention was made for the person of ordinary skill in the art to have modified Heller's methods with improvement of an unwanted probe as taught by Elsas in further view of a probe B with a 5' terminus donor and 3' terminus acceptor moieties as taught by Meade. Heller teaches a Probe B with a quencher at its 5' terminus and specifically teaches that the acceptors and donor pairs with different emission spectrums (column 6, lines 63-67 through column 7, lines 1-9; column 7, lines 2-11 and 32-34). The ordinary artisan at the time the invention was made would have been motivated to modify Probe B with a fluorophore at the 3' terminus of a different fluorescence because the skilled artisan would be able to specifically distinguish between the presence of the target "wanted" sequence Probe A as indicated by the amount of its fluorescence, and the exact, unambiguous hybridization "unwanted" control sequence of Probe B (Meade, page 11, left column, paragraph 0123) because the fluorophores on each probe has a different emission spectrum (Heller, column 7, lines 2-11 and 32-34).

9. Claims 2-11 and 15-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heller (U.S. Patent No. 5,532,129, published July 1996) and Elsas et al (U.S. Patent No. 6,207,387, published March 27, 2001) as applied to claims 1, 12, 13, and 21, and further in view of Oliveira et al. (Journal of Clinical Microbiology, January

2002, Vol. 40, No. 1, pages 247-251) in view of GenBank S83568 (published September 22, 1993) in further view of Hogan et al. (WO0066788, published November 11, 2000).

Heller teaches a method to detect target sequences, wherein the method comprises step a) hybridizing two probes, wherein one probe has a fluorophore (Probe A) and another probe that has a quencher (Probe B) that hybridizes adjacent to Probe A; and method step b) the subsequent detection of Probe A's fluorescence as an indication of the presence of a target sequence.

With respect to method step 1, Heller teaches a method comprising contacting two probes with a configuration wherein Probe A is labeled with a donor group at its 3' terminus and Probe B is labeled with an acceptor at its 5' terminus, and are hybridized adjacent to one another (Figure 1B). Heller's method includes "hybridization [of the probes] to the target sequence ... the fluorescent donor group...and acceptor group to a preselected donor-acceptor transfer distances so that when the system is irradiated by photonic energy at hv_1 the donor group absorbs the energy and transfers it...to the acceptor group which re-emits at (hv_2)," wherein Probes A and B have donor and acceptor groups respectively (column 4, lines 24-31). Heller teaches Probe B's acceptor group is a quencher and "use of quencher chromophore (or quencher)...has the capacity to accept...the transfer of energy...but does not have significant emission (column 6, lines 63-67 through column 7, lines 1-9). Thereby, Probe B's quenching group results in the lack of emission (hv_2). Accordingly, Heller teaches a 3' fluorophore, or donor, at the 3' termini of Probe A, and quencher, or acceptor, at the 5' end of Probe

B. Furthermore, Heller teaches another configuration of the placement of the fluorophore and quencher groups on Probes A and B. Heller teaches Probes A and B can be labeled internally and spacing between the donor and acceptor groups can be from 0-7 basepairs (column 10, lines 12-14 and 34-35; column 11, lines 17-19). Heller teaches that the probes can be configured in that there is "any chromophore can be paired with another chromophore to form an acceptor-donor pair, so long as the two chromophores have different emission spectrums," wherein the choromphores are defined as either fluorophores or quenchers (column 7, lines 2-11 and 32-34).

With respect to method step b, Heller teaches the level of hybridization to the target sequences is measured by the amount of Probe A's fluorescence. Heller teaches "relative efficiencies for the energy transfer process can be expressed...in terms of the ratio of transferred energy to the energy absorbed by the donor; this is determined by measuring the relative amount of donor fluorescence quenching that occurs in the presence of the acceptor" (column 6, lines 27-32).

However, Heller does not teach the application of peptide nucleic acid (PNA) probes with sequences of SEQ ID NO: 1 and 2 designed for wanted and unwanted sequences, to detect antibiotic resistant species of bacteria in cell or tissue samples. Moreover, Heller does not teach a method in which said samples are manipulated to preserve the target sequence, and the presence of SEQ ID NO: 1 and 2 in said samples are detected with fluorescent in situ hybridization (FISH).

Elsas teaches of anchor and detection probes that detect mutations. Elsas teaches determining different mutations "can be achieved by using oligonucleotides...by

attaching different detectable moieties, such as fluorescent, chemiluminescent, bioluminescent...to the oligonucleotides" (column 10, lines 43-47). Elsas teaches anchor and detection probes, wherein the "anchor probe forms one half of the detection probe set and carries a fluorescence quencher. The other half of the probe set has the allele-specific sequence. When the allele specific probe and the anchor probe are hybridized, the fluorescence is quenched" (column 11, lines 2-7). Detection probes are designed for a wherein "the lower case letter represents the nucleotide that is different between the mutated and wild-type alleles" (column 10, lines 63-67 through column 11, lines 1-7). Thus, Probe A is the detection probe because it has both "wanted" and "unwanted" sequences, wherein the "wanted" sequence, the nucleotide of interest represented by the lowercase letter, and the sequences flanking the lower case letter is the "unwanted" sequences that correspond to the wildtype sequence. Similarly, Probe B is represented by the anchor probe because it has a quencher that hybridizes to the wild-type sequence, or "unwanted" region. The detection probe, Probe A, inherently has a fluorophore because the anchor probe quenches fluorescence during hybridization.

However, Elsas does not teach PNA wanted and unwanted probes of SEQ ID NO: 1 and 2 with fluorophores and quenchers to detect antibiotic resistant species of bacteria in cell or tissue samples. Moreover, Elsas does not teach a method to apply said probes to said samples that were manipulated to preserve a target sequence. Elsas also does not teach a method wherein the presence of SEQ ID NO: 1 and 2 in said samples are detected with FISH assays.

Oliveira teaches a method that distinguishes bacteria of clinical interest that are antimicrobial resistant with FISH assays that use PNA probes, wherein Oliveira's method comprises: 1) obtaining a blood sample; 2) fixing said sample and samples of reference bacterial strains to microscope slides; 3) probing all of said samples with a *Staphylococcus aureus* (S. *aureus*) PNA probe; and 4) identifying the bacterial species in said sample with FISH. In particular, Oliveira differentiates several species bacteria. Oliveira teaches a "FISH method with peptide nucleic acid (PNA) probes for identification of *Staphylococcus aureus*...The test....is based on fluorescin-labeled PNA probe that targets a species-specific sequence of the 16S rRNA of S. *aureus*. Evaluations [were done] with 17 reference strains and 48 clinical isolates, including methicillin-resistant and methicillin-susceptible S. *aureus* species...and other clinically relevant and phylogenetically related bacteria" (abstract).

With respect to claim 2, Oliveira teaches a detection method with FISH assays (abstract, line 1).

With respect to claims 3 and 4, Oliveria teaches Oliveira specifically uses PNA probes due to their high specificity. Oliveira teaches "PNA probes exhibit favorable hybridization characteristics such as high specificity, strong affinities, and rapid kinetics, resulting in improved hybridization to highly structured targets such as rRNA. In addition, the relatively hydrophobic character of PNA compared to that of DNA oligonucleotides enables PNA probes to penetrate the hydrophobic cell wall of bacterial" (page 247, right column).

With respect to claim 5, 6, 8, and 10, Oliveira teaches "fluorescin-labeled PNA probe" that comprises, consists essentially, and has the instant SEQ ID NO: 1. Oliveria teaches SEQ ID NO: 1 "target[s] S. *aureus*16S rRNA," wherein SEQ ID NO: 1 has 15 subunits in length (page 248, left column). Oliveira targets rRNA sequences because "it is a well established method for phylogenetic analysis of microorganisms, and the sequence variations found between the relatively conserved rRNA sequences form the basis for the design of probes specifically for most bacteria" (page 247, right column).

With respect to claim 16, Oliveira teaches the target is obtained from blood cultures, which inherently contain cells (page 248, left column).

With respect to claims 17 and 18, Oliveira teaches the samples were "fixed [to sides] by passing the slide through the blue cone of a Bunsen burner three to four times or by treatment with methanol" (page 248, left column).

With respect to claim 19 and 20, Oliveira teaches "the sensitivity and specificity of the S. *aureus* PNA FISH assay...examined with 48 clinical isolates representing methicilliin-resistant and methicillin-susceptible S. *aureus* strains" and from sixteen other bacterial species, and "the assay correctly identified all S. *aureus* isolates," wherein one of the clinical microorganisms includes *S. schleiferi* (page 249, left column, and Table 1, page 250).

However, Oliveira does not teach a method of using a PNA probe with SEQ ID NO: 2 to detect microbial resistant bacteria, nor a probe with SEQ ID NO: 1, wherein said probes are labeled with fluorophores or quenchers. Oliveira also does teach the

application of said PNA probes to preserved samples to detect the presence of SEQ ID NO: 1 and 2 with FISH assays.

GenBank S83568 teaches a nucleic acid sequence that is the reverse complement of the instant SEQ ID NO: 2 at basepairs 83-97 (claim limitations 7, 9, and 11). GenBank S83568 teaches is isolated sequence of 16S rRNA from *S. schleiferi* (definition).

However, GenBank S83568 does not teach the application of S83568 as a labeled PNA probe to detect microbial resistant bacteria with a labeled PNA probe of SEQ ID NO: 1. Further, GenBank S83568 does not teach a method wherein said probes are used to detect said bacteria with FISH assays.

Hogan teaches the use of species specific PNA probes to distinguish different Staphylococcus bacteria from one another. Hogan teaches "probes, which are complementary to particular rRNA sequences of the 16S rRNA, advantageously are capable of distinguishing Staphylococcus organisms from the known phylogenetically nearest neighbors...Variable regions of rRNAs...[are] identified by comparative analysis using published rRNA sequences" wherein "commercially available software can be used" to design probes (page 12, lines 8-10 and page 14, lines 20-23). In particular, Hogan teaches that said probes can be PNA (page 18, lines 1-8).

With respect to claims 5-11, 19 and 20, it would have been obvious at the time the invention was made for the ordinary artisan to have modified Heller's method with the improvement of probes with "wanted" and "unwanted" sequences of SEQ ID NO: 1 and 2 as taught by Elsas to distinguish microbial resistant bacteria species in a sample

as taught by Oliveiria, Genbank S83568, and Hogan. One skilled in the art at the time the invention was made would have been motivated to have modified Heller's sensitive sequence detection method with to detect the variable "wanted" species specific sequences that distinguishes *S. aureus* from *S. schleiferi*. With a probe of SEQ ID NO: 1, Oliveira teaches it can be utilized to distinguish *S. aureus* from *S. schleiferi*. Oliveira teaches that with the PNA probe of SEQ ID NO: 1, the "results indicate that the assay has a high degree of specificity, with the only limitation being a weak cross-hybridization to *Staphylococcus schleiferi*....the PNA probe has only a single mismatch to some *S. schleiferi* 16S rRNA sequences" (page 248). The prior art teaches 16S rRNA sequences are highly specific to bacteria strains and are utilized to distinguish Staphylococcus species from one another (Oliveira and Hogan as cited above). As mentioned previously, GenBank S83568 teaches an isolated sequence of SEQ ID NO: 2 from 16S rRNA of *S. schleiferi*. By screening for "wanted" and "unwanted" Staphylococcus species specific sequences with PNA probes, the skilled artisan at the time the invention was made could identify the mismatch in the 16S rRNA region responsible for methicillin-resistance with probes of SEQ ID NO: 1 and 2, sequences that are associated with *S. aureus* and *S. schleiferi* respectively. It would have been obvious to one skilled in the art at the time the invention was made to have used a probe with SEQ ID NO: 2 in order to achieve the benefit a performing diagnostic assays with a "unwanted" or control *S. schleiferi* specific probe in addition to the *S. aureus* specific probe of SEQ ID NO: 1. In order to detect the mismatch that differentiates *S. aureus* and S. schleiferi, wherein Probe A is designed for the "wanted" mismatch that

differentiates *S. aureus* from *S. schleiferi* as detected by SEQ ID NO: 1, and Probe B is the "unwanted" control sequence for *S. schleiferi* (Heller, column 3, lines 1-3; Elsas column 11, lines 1-7; Oliveira, page 248; Genbank S83568). Accordingly, the skilled artisan would have probes specific for their respective species to used to discriminate between specific mutations. The skilled artisan would have been motivated to have performed such an assay with SEQ ID NO: 1 and 2 so as to provide optimal antibiotic treatments to patients with a *S. aureus* infection as opposed to an infection of *S. schleiferi* (Oliveira, abstract and page 248). In particular, the skilled artisan would have been motivated to have used a probe with SEQ ID NO: 1 in order to achieve the benefit of detecting *S. aureus* methicillin drug resistant bacteria from other related bacteria in order to prescribe a more appropriate, effective non-methicillin antibiotic to patients with *S. aureus* infection to attain an "optimal antibiotic therapy" (Oliveira, abstract). Thus, with Heller's sensitive assay method and Elsa's probe design, Probe A would have the wanted and unwanted sequence of SEQ ID NO: 1 as it has the "wanted" sequence allele and "unwanted" flanking wildtype sequence of *S. aureus*, and Probe B with the unwanted sequence of *S. schleiferi.*

With respect to claims 2-4, and 16-18, it also would have been obvious at the time the invention for the ordinary artisan to have modified Heller's method with the improvement of a PNA probe of SEQ ID NO: 1 and 2 in order to identify antimicrobial resistant bacterial strains in samples with FISH assays, wherein the "wanted" sequence can differentiate *S. aureus* from *S. schleiferi* as taught by Elsas and Oliveria and Genbank S83568 and Hogan. The improved method of Heller with allele detection

probes allows for sensitive diagnostic assays (Heller, column 3, lines 1-3, and Elsas column 11, lines 1-7). Oliveira teaches PNA probes have higher specificity, stability, and faster hybridization rates than oligonucleotide probes (page 247). Moreover, Oliveira also teaches that the hydrophobic properties of PNA probes allows for better hybridization to bacterial cell walls when said bacteria are fixed in FISH assays (page 247). The skilled artisan at the time the invention was made would have also been motivated to have used PNA probes in order to achieve the benefit of a rapid, highly specific hybridization of probes to detect microbes (Oliveira, page 247). One would have been motivated to have used PNA probes for their high specificity to detect "wanted" unique, species specific rRNA sequences because of their ability to penetrate bacterial cell walls, which would have been more difficult to achieve with natural oligonucleotide probes (Oliveira, page 247, right column). One skilled in the art at the time the invention was made would have also been motivated to have used the PNA probes of SEQ ID NO: 1 and 2 with a FISH assay because Oliveira teaches it is "routinely used for the identification of *S. aureus*" (page 247).

With respect to claim 15, one skilled in the art at the was claimed to have modified Heller's sequence detection method with the PNA probes of SEQ ID NO: 1 and 2 which are separated by 1-5 nucleotide bases with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because Heller teaches that the probes hybridize in close proximity to one another by 0-7 basepairs in order to have a sensitive assay (column 10, lines 12-14, and lines 34-41).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The current claims are drawn towards nucleic acids comprising, consisting essentially, and having SEQ ID Nos: 1 and 2.

The specification has only described nucleic acids consisting of SEQ ID NO: 1, and the nucleic acids consisting of SEQ ID No: 2. Thus, applicant has express possession of only isolated nucleic acids which consist of SEQ ID NO: 1 and 2. The claims recite "comprising", "consisting essentially" and "has" the following sequences of SEQ ID NO: 1 and 2. The claims encompass a large genus of sequences, including sequences with additional sequences flanking SEQ ID NO: 1 and 2 from any source. The specification does not provide guidance as to what constitutes SEQ ID NO: 1 and 2, and the claims provide no indication of the limits of their structural identity.

With regard to the written description, these claims encompass nucleic acids different from those disclosed in the specific SEQ ID Nos: 1 and 2. The nucleic acids

comprising, consisting essentially, and have SEQ ID NO: 1 and 2 are not synonymous with microbial resistant bacteria. For example, a prior art search of sequences that comprise, consist essentially, and have SEQ ID NO: 1 are embedded within a thermostable endonuclease (Kaiser et al., US Patent No. 5,843,669, December 1, 1998, SEQ ID NO: 160) and the mosquito *Anopheles gambiae* (GenBank Accession No. CNS01M9N, published June 14, 2001). A post-filing sequence search indicates that SEQ ID NO: 1 is isolated from cows (GenBank Accession No. BZ846224, published March 13, 2003). Likewise, a sequence search of nucleic acids that comprise, consist essentially, and have SEQ ID NO: 2 makes it clear that a nucleic acid with said sequences are embedded in the plant *Arabidopsis thaliana* (Alexandrov et al., EP1033405, published September 6, 2000, SEQ ID NO: 18779), and a prostate specific membrane antigen 18 coding sequence (Mao et al, WO200173062, published October 4, 2001, pages 31-32). Similarly, a post-filing sequence search of SEQ ID NO: 2 teach that it is found in rats (Zhou, USPGPUB 20040146910, published July 29, 2004, SEQ ID NO: 571413), and rice (La Rosa, et al., USPGPUB 20040123343, published June 24, 2004, SEQ ID NO: 97628).

The art which teaches sequences comprising, consisting essentially, and have SEQ ID NO: 1 and SEQ ID NO: 2 are associated with sequences with different functions and are isolated from a variety of species does not provide for a structure which is correlative of a common function in the large variable genus of sequences encompassed. This represents a large variable genus of polynucleotides, with little

structural similarity. The specification fails to provide an adequate description of a representative number of species of this large variable genus.

It is noted in Fiers v. Sugano (25 USPQ2nd, 1601), the Fed. Cir. Concluded that

> "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method for obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

In the instant application, only sequences consisting of SEQ ID NO: 1 and 2 are described. Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception or written description of sequences comprising, consisting essentially, and having SEQ ID NO: 1 and 2.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-21 are indefinite over the recitation of "wanted and unwanted." "Wanted and unwanted" is not an art recognized term to describe a particular sequence. Because the terms "wanted and unwanted" has not been clearly defined in the specification and because there is no art recognized definition for this term as it relates to the sequences, one skilled in the art cannot determine the meets and bounds of the claimed invention.

B) Claims 1-21 are indefinite over the recitation of "closest." "Closest" is not an art recognized term to describe the placement of moieties on two probes that hybridize to one another. Since closest is a relative term, It is unclear if closet is defined as the moieties are immediately adjacent to each other, or in reference a particular position in the probe. Because the term "closest" has not been clearly defined in the specification and because there is no art recognized definition for this term as it relates to the sequences, one skilled in the art cannot determine the meets and bounds of the claimed invention.

C) Claims 1-21 are indefinite over the recitation of "from about." From about is not an art recognized term to describe the distance between two hybridized probes. The claims recite that Probes A and B are separated "from about one to five" nucleotides. It is unclear if "from about" encompasses a distance consisting or comprising one to five

basepairs. For instance, it is unclear if the probes can be separated from each other by 7 or 9 basepairs are applicable to the methods of the claimed invention because 7 and 9 basepairs are "about" five nucleotides. Because the term "from about" has not been clearly defined in the specification and because there is no art recognized definition for this term as it relates to the sequences, one skilled in the art cannot determine the meets and bounds of the claimed invention.

Conclusion

12. No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Wong whose telephone number is (571) 272-1120. The examiner can normally be reached on Monday-Friday; 8 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jennifer Wong

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4/27/06